REMARKS/ARGUMENTS

Claims 1, 5, 8, 16, and 17 are pending in this application. Claim 1 has been amended to better claim the subject matter which Applicants regard as the invention. Claims 5, 8, and 16 have been amended to correct dependency. Claims 2, 7, 9-15, 18, and 21-25 have been canceled without prejudice. Claims 3-4, 6, and 19-20 had previously been canceled without prejudice. No new matter has been added with this Amendment.

Claims Rejections under 35 U.S.C. § 103:

Claims 1-2, 5, 7, 12-16, 18, and 24 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Anselem et al. (US Patent 5,716,637) in view of Glenn et al. (US Patent 5,980,898). Applicants respectfully traverse the rejection.

Without acquiescing to this rejection and in the interest of advancing prosecution of this application, claims 2, 7, 12-15, 18, and 24 have been canceled without prejudice.

The Office Action states:

> "Anselem teaches nanoemulsions comprising nanoparticles containing antigenic particles. Anselem's compositions are useful for inducing an immunogenic response via topical route. The emulsome particles of Anselem do not contain an adjuvant. The antigenic particles of Anselem can include chemically or physically inactivated particles of virus, such as Hepatitis B surface antigen, or bacteria such as Leishmania. Thus, Anselem teaches topical immunization of a subject by using a composition comprising an antigenic nanoparticulate."

Anselem et al. teaches the use of solid fat nanoemulsions as vaccine delivery vehicles. The nanoparticles have a lipid core and an antigen incorporated intrinsically or extrinsically therein. The antigen that is incorporated into the nonaparticles is a peptide, a protein, a glycoprotein, polysaccharides, glycolipids, or any peptide or protein antigens derived from bacteria, viruses and parasites. In some cases, the peptide

antigens are inactivated chemically or physically (see from column 10, line 57 to column 11, line 18). The nanopaticles have a mean diameter in the range of 10 to 250 nm.

In contrast, the invention claimed herein is a method of inducing an immune response by applying intact virus particles of diameter in the range of 50 to 200 nm to the unbroken surface of the skin without the use of an adjuvant. Anselem et al. does not suggest the use of an intact virus particle as an antigen. When an antigen is a viral peptide or protein to be incorporated into the nanoparticles in Anselem et al., such peptide or protein is derived from a virus (e.g., envelope protein). Nor does Anselem teach or suggest an antigen of the size between about 50 to 200 nm which can be incorporated into the nanoparticles. There is no suggestion that the topical use, merely mentioned therein, is meant to indicate the application of the nanoparticles on the unbroken surface of the skin. The Office Action acknowledges that Anselem does not explicitly provide the administration of his compositionns on an unbroken surface. The nanoparticles described in Anselem et al. and the virus particles useful for inducing an immune response in the present case represent two distinct types of immune compositions. Accordingly, Anselem et al. does not suggest the invention nor motivates a person of ordinary skill in the art to combine the teachings therein with the teachings of Glenn et al. to make the invention, as alleged by the Examiner.

The Office Action further states:

> "Glenn et al. teaches a transcutaneous immunization formulation comprising antigen to unbroken skin and without perforation of the skin induces an immune response.
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> "Glenn et al. further teaches that the antigen may be further derived from a virus. Glenn et al. also teaches that an antigen may be in the form of an inactivated virus and be incorporated in a liposome before administration. Among the viruses that can be used in the practice of the invention Glenn teaches hepatitis, influenza, and measles. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to use Anselem's emulsomes containing an antigen on an unbroken surface of skin, as taught by Glenn. The ordinary skill in the art would have been

motivated to do such application of Anselem's composition because as suggested by Anselem himself, topical delivery of such antigens are possible for inducing an immunogenic response and further, as suggested by Glenn, one of ordinanry skill in the art would have had a reasonable expectation of success to provide a transcutaneous immunization through an unbroken skin surface."

Applicants emphasize that the invention claimed is a method for inducing an immune response using a particulate antigen of inactivated or attenuated virus particles of diameter from about 50 to 200 nm without the use of an adjuvant. The Glenn patent describes a method of immunization using a combination of an antigen and an adjuvant. The antigens in Glenn et al. are soluble proteins (e.g. toxins and toxoids) derived from various pathogens (see column 16, lines 48-61). There is nothing in the cited patent which suggests that an effective immunization can be achieved by administering particulate antigens without the aid of an adjuvant, particularly large viral particles of diameter about 50-200 nm, on the intact surface of the skin. As discussed above, nothing in Anselem et al. suggest the invention as claimed or provides motivation to a person of ordinary skill in the art to combine the teachings therein with the teachings of Glenn et al. to make and/or use the invention. Even if one were to combine the teachings of the two references, one cannot make the invention.

The present invention is the first actual experimental demonstration that the administration of the particulate antigens of relatively large size alone (i.e., virus particles not combined with an adjuvant) is sufficient to provide protective immunity. The cholera toxin described in Glenn et al. has a molecular weight of about 87 kDa. The influenza virus particle exemplified in the present application has a particulate weight of about 250,000 kDa and a particle diameter of about 100 nm. Accordingly, this virus has a weight nearly 3000-fold larger than that of cholera toxin or bovine serum albumin. Surprisingly, the inventors discovered that the virus particles could penetrate the unbroken skin and come in contact with immune cells so that not only virus-specific immunoglobulins were produced, but protective immunity is also resulted, in the absence of any adjuvant. The state of the art at the time the present invention was made was such that the method claimed herein was not expected to induce an efficient immune response. Without the actual experimental demonstration of successful

protective immunity by the inventors, there is no reason for a skilled artisan to expect that the method of immunization as claimed would work.

In summary, based on the above remarks and amendment, claims 1, 5, and 16 are not *prima facie* obvious over Anselem et al. in view of Glenn et al. Withdrawal of the rejection under Section 103(a) is respectfully requested.

Claims 2, 5, 7-18, and 21-25 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Anselem et al. in view of Glenn et al. and further in view of Fields et al. Applicants respectfully traverse this rejection.

The Office Action states:

> "....neither Anselem or Glenn explicitly describe the use of Formalin for inactivation of the particle, nor do they mention that influenza virus contains hemogglutinin (HA) and that such virus is a orthomyxovirus. Fields et al. teaches that HA is the major antigen of influenza virus, a known orthomyxovirus. Fields also teaches that semi-purified influenza virus subunit vaccines containing the HA surface antigens of the virus are less toxic than are activated whole virus vaccines. Fields also teaches a method of inactivating viruses employing formalin...."

Without acquiescing to this rejection and in the interest of advancing prosecution of this application, claims 2, 7, 9-15, 18, and 21-25 have been canceled without prejudice. Accordingly, certain issues raised above are no longer relevant.

As pointed out in the previous Response, Fields et al. is a general reference that provides a brief description of licensed vaccines, live and non-living, in the United States. The use of formalin for inactivating virus particles is not new. The non-obviousness of the invention lies in the combination of the factors to make the invention, i.e., the large size of the particulate antigens (intact viral particles of about 50-200 nm in diameter) and the administration of such large particles onto the unbroken skin without the use of an adjuvant to induce an immune response. In this regard, the Field reference has little bearing on the claimed invention. The invention as claimed should

be viewed as a whole. For the reasons discussed above, neither Anselem et al. nor Glenn et al. suggest the invention or provide motivation to one of ordinary skill in the art to combine the teachings therein to make the invention.

Based on the foregoing, claims 5, 8, 16, and 17 are not *prima facie* obvious over Anselem et al. in view of Glenn et al. and Fields et al. Withdrawal of the rejection under Section 103(a) is respectfully requested.

Conclusion:

Based on the foregoing amendments and arguments, this application is considered to be in condition for allowance and passage to issuance is respectfully requested.

If there are further issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

It is believed that this submission does not require the payment of any fees. However, if this is incorrect, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,

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